

g) detecting and optionally measuring the concentration of the HIV proteins, either directly or indirectly.

REMARKS

Applicants file this Amendment in reply to the February 9, 2002, Office Action where the Examiner indicated that there was a typographical error in the claim amendments in Applicants' November 20, 2001, reply. Applicants have corrected the error in the marked-up version of claim 2, as suggested by the Examiner. Applicants have also replaced the word "or" with the word "and" in claim 6 to use proper claim formatting. Otherwise, this Amendment is identical to the one filed on November 20, 2001, and complies with Applicants' duty to file a corrected response. Applicants appreciate the Examiner's careful attention to the file, noticing the error, and recognizing that Applicants had filed a *bona fide* reply.

Claims 2, 4, 5, 6, 9, 10, 13 and 23 have been amended in this application. No new matter has been added to this application by way of these amendments, and support for the amended claims may be found in the original claims and throughout the specification.

Objections to the specification and to the claims are obviated by the amendments presented in this response. The claims have been amended to remove non-elected subject matter and to recite the term "any one" instead of "anyone." The improper multiple dependencies have also been corrected. Therefore, withdrawal of these objections is respectfully requested.

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The Examiner objected to the title on page 64 of the specification, requesting that the term "Figures" be replaced by the phrase --Brief Description of the Drawings--. Applicants have made the requested change. Additionally, the Examiner requested that Applicants correct the drawings to add SEQ ID NOs where necessary. Applicants will prepare and file corrected drawings when allowable subject matter has been indicated.

Indefiniteness Rejections

Claims 2-6, 9-10, and 13 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. The Examiner rejected claim 2 for recitation of "**peptidic or non-peptidic variants.**" Applicants submit that these terms are not indefinite. The term "peptidic" is listed in The American Heritage College Dictionary (3rd ed) as the adjective form of the noun peptide, which means any of various natural or synthetic compounds containing two or more amino acids linked by the carboxyl group of one amino acid and the amino group of another. The adjectives "peptidic" and "non-peptidic" describe the inhibitor molecule, a compound that is able to modify the interaction between the HIV receptor and the gp120 envelope glycoprotein, and clarifies that the inhibitor can be a peptide or a non-peptide. Applicants believe that the claimed language would be easily understood by one of ordinary skill in the art.

The Examiner also rejected claim 2 as containing allegedly indefinite claim terms, such as "**modify the interaction,**" "**on the one hand . . . on the other hand**," "**present on the cell surface**," and "**human HIV retrovirus.**" While Applicants believe these claim terms would be understood by the skilled artisan, the terms have been replaced by alternate language in amended claim 2.

Claim 3 has been rejected as indefinite for reciting "**peptide fragment**." The Examiner questioned the meaning of the term peptide fragment, and asked whether the term "peptide fragment" is different from the term protein fragment. The term peptide fragment refers to a fragment of an HIV receptor, wherein the fragment is a peptide. To clarify the claim language, Applicants have amended the claim to use the adjective "peptidic" instead of the noun "peptide" to make it clear that the fragment is a peptide.

The Examiner also rejected claim 3 for containing the allegedly indefinite term "**pseudopeptide counterpart**". Pseudopeptides are described in the specification as compounds, such as 5[Kψ(CH₂N)PR]-TASP, where TASP stands for "template assembled synthetic peptide". The synthesis of the pseudopeptide TASP constructs are described in the Examples, starting on page 95, and are known in the art.

Applicants have enclosed the reference *Callebaut, Inhibition of HIV Infection by Pseudopeptides Blocking Viral Envelope Glycoprotein-Mediated Membrane Fusion and Cell Death, Virology 218:181-192 (1996)*, which further describes these compounds.

The pseudopeptide TASP constructs are assembled using a lysine-rich short peptide as a template to covalently anchor arrays of tripeptides. The term "counterpart" refers to the fact that the peptidic fragment and the pseudopeptide could have structural and/or functional homology.

The Examiner has also rejected claim 4 as containing the allegedly indefinite language "**which consists in a peptide or pseudopeptide which is homologous**." Applicants have rewritten the claim to clarify that inhibitor molecule of claim 4 is homologous to the inhibitor of claim 3. The inhibitor of the present claim is homologous

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in that it has sequence homology to the inhibitor of claim 3, but not identical in that it has at least one amino acid sequence addition, deletion, or substitution.

The Examiner has also rejected claim 5 for use of the phrase "**peptide bond is modified and replaced.**" Amended claim 5 does not recite the objected-to "modified" language, thus obviating this rejection. Also, the claim indicates which peptide bond should be replaced, and Applicants respectfully submit that an indefiniteness rejection on this basis is improper.

All other rejections based on 35 U.S.C. § 112, second paragraph, for alleged indefiniteness have been obviated by cancellation of the pending claims and removal of the objected-to language in the amended claims presented in this response. In light of the amendments and arguments presented above, reconsideration and withdrawal of these indefiniteness rejections are respectfully requested.

Anticipation and Obviousness Rejections

Suzuki Reference

The Examiner has rejected claims 2-4, 6, 10, and 13 under 35 U.S.C. § 102(b) as anticipated by *Suzuki et al.*, or in the alternative under 35 U.S.C. § 103 as obvious over *Suzuki et al.* The Examiner asserts that *Suzuki* discloses a method which generates fragments of nucleolin the same as or similar to those claimed in the present application. The Examiner believes that the entire nucleolin protein was digested and would produce all of the peptides of the present invention. Using the peptides for the

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inhibition of gp120/nucleolin binding would allegedly be an inherent feature of the fragment.

Applicants have considered the *Suzuki* reference. *Suzuki* discloses nucleolin fragments of the N-terminal end of the full protein that were isolated from rat liver cell nucleoli, i.e., nuclear nucleolin sequences, not nucleolin that takes part in cell surface interactions between HIV and the gp120 glycoprotein in human cells (i.e., cell surface expressed nucleolin). The specification of the present application shows that these two proteins are distinguishable. In Example 12, the inventors performed assays to characterize the differences between nuclear nucleolin and cytoplasmic or cell surface expressed nucleolin (which has been given the name P95/nucleolin by the inventors). (Specification, page 119, Example 12). Two dimensional gel isoelectric focusing experiments showed that nuclear nucleolin was composed of several related species with a pI of between pH 4.5 and 5.5. On the other hand, P95/nucleolin in the cytoplasm or expressed on the cell surface has a pI value at about 4.5. (*Id.*) The results of this experiment can be seen on Figure 12. Additionally, while the 60 kD portion of the nuclear nucleolin of *Suzuki* originates in the N-terminal region of the nuclear nucleolin molecule (*Suzuki*, abstract), the 60 kD portion of the cell surface nucleolin of the invention originates in the C-terminal region of the cell surface nucleolin molecule.

Hovanessian, The Cell-Surface-Expressed Nucleolin Is Associated With The Actin Cytoskeleton, Experimental Cell Research 261:312-328, at 318 left column (2000).

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Applicants have clarified that they do not intend to claim the nuclear nucleolin of the prior art. Therefore, *Suzuki* does not anticipate the claimed P95/nucleolin inhibitor molecule, or fragments of that molecule.

Also, the *Suzuki* reference does not render the P95/nucleolin inhibitory molecule of the present invention obvious under 35 U.S.C. § 103(a). As we have discussed, the P95/nucleolin of the present invention is only cell surface expressed P95/nucleolin, not the nuclear nucleolin of the prior art. Additionally, in this rejection the Examiner does not account for the fact that the *Suzuki* reference does not teach or suggest the existence of a nucleolin that functions extracellularly, nor does it indicate potential HIV inhibitory characteristics of human nucleolin.

Therefore, reconsideration and withdrawal of these anticipation and obviousness rejections are hereby respectfully requested.

Sapp Reference

Claims 2-4, 6, 9-10, and 13 are rejected under 35 U.S.C. § 102(b) as anticipated by or under 35 U.S.C. § 103(a) as obvious over *Sapp et al.* Specifically, the Examiner argues that *Sapp* also discloses a method for generating nucleolin fragments, that the entire protein was digested, and that the method disclosed by *Sapp* would generate the peptide or fragments claimed by the Applicants. Applicants respectfully traverse these rejections, and reconsideration and withdrawal are respectfully requested.

Sapp, like *Suzuki*, teaches isolation of nucleolin from nucleoli. *Sapp* teaches isolation of what the authors believed was 2/3 of the full protein (containing the carboxy-

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terminus) from calf thymus cell nucleoli. As we have discussed above, the present invention is not directed to the nuclear nucleolin of the prior art. Cytoplasmic and cell surface expressed nucleolin have a different isoelectric point and can be distinguished from the nuclear nucleolin of the prior art.

Furthermore, there is no indication that the fragment of nuclear nucleolin described in *Sapp* contains the claimed HIV inhibitory activities of the present invention on human cells. Also, the *Sapp* reference teaches the potential importance of the isolated protein fragment in rRNA packaging, rDNA activation (histone activity), and ribosome assembly (see 541, last sentence, ¶ 2). Thus, the *Sapp* reference to the isolated carboxy-terminus fragment of calf thymus nuclear nucleolin does not anticipate the HIV inhibitory cell surface nucleolin molecules of the present invention.

Additionally, the present invention would not have been obvious from the teachings of the *Sapp* reference for the same reasons it would not have been obvious from the *Suzuki* reference. As we have discussed above, the claims no longer read on nuclear nucleolin, which is a different structure than cytoplasmic or cell surface expressed P95/nucleolin. The reference does not teach or indicate the existence of nucleolin that functions extracellularly, nor does it indicate potential HIV inhibitory characteristics of human nucleolin. For the foregoing reasons, reconsideration and withdrawal of the rejections based on the *Sapp* reference are respectfully requested.

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PATENT
Customer No. 22,852
Application No. 09/393,302
Attorney Docket No. 3495.0166-01

Srivastava Reference

Claims 2-6, 9-10, and 13 are rejected under 35 U.S.C. § 103 (a) as obvious over Srivastava et al. Srivastava discloses a human nucleolin cDNA sequence and the associated amino acid sequence. As we have discussed above, the claims no longer read on nuclear nucleolin, which is a different structure than cytoplasmic or cell surface expressed P95/nucleolin. Therefore, withdrawal of this obviousness rejection is hereby respectfully requested.

Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims. Should the Examiner feel that the claims are not in condition for allowance, Applicants request that he contact the undersigned representative at 202-408-4086 to arrange for an interview to discuss the invention.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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Dated: February 26, 2002

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APPENDIX TO AMENDMENT
IN REPLY TO THE FEBRUARY 9, 2002 OFFICE ACTION

IN THE SPECIFICATION:

Page 64, line 12, delete heading [Figures] and insert heading Brief Description of the Drawings.

IN THE CLAIMS:

2. (Amended) A peptidic or non peptidic inhibitor molecule that is able to [modify] alter and/or prevent the interaction between[, on one hand the purified] a receptor [according to claim 1 present at the cell surface of a patient infected with a human HIV retrovirus, specifically HIV-1 or HIV-2] located on the surface of an HIV infected cell and [on the other hand the] a gp120 envelope glycoprotein of said HIV retrovirus, wherein the inhibitor is not nuclear nucleolin.

4. (Amended) [The] An inhibitor molecule [of claim 2 which consists in] that is homologous to the inhibitor molecule of claim 3, wherein said inhibitor molecule comprises a peptide or pseudopeptide [which is homologous] containing [one or several] at least one amino acid [additions] addition, [deletions] deletion, [and/or substitutions] or substitution in the amino acid sequence [of the inhibitor molecules according to claim 3].

5. (Amended) The inhibitor molecule according to [anyone] any one of claims [1] 2 to 4 in which [the] a -CONH- peptide bond is [modified and] replaced by a [(CH₂NH)] (-CH₂NH-) reduced bond, a [(NHCO)] (-NHCO-) retro inverso bond, a [(CH₂-O)] (-CH₂-O-) methylene-oxy bond, a [(CH₂-S)] (-CH₂-S-) thiomethylene bond, a

[(CH₂CH₂)] (-CH₂CH₂-) carba bond, a [(CO-CH₂)] (-CO-CH₂-) cetomethylene bond, a [(CHOH-CH₂)] (-CHOH-CH₂-) hydroxyethylene bond, a [(N-N)] (-N-N-) bond, a E-alcene bond, or [also] a [-CH=CH-] (-CH=CH-) bond.

6. (Amended) The inhibitor molecule according to [anyone] any one of claims [1] 2 to 5, which [is derived from the P95/nucleolin amino acid sequence and chosen among] comprises amino acid sequences selected from the following P95/nucleolin sequences:

- the sequence beginning at the amino acid in position 22 and ending at the amino acid in position 44 of SEQ ID NO: 1;
- the sequence beginning at the amino acid in position 143 and ending at the amino acid in position 171 of SEQ ID NO: 1;
- the sequence beginning at the amino acid in position 185 and ending at the amino acid in position 209 of SEQ ID NO: 1; and
- the sequence beginning at the amino acid in position 234 and ending at the amino acid in position 271[; of SEQ ID NO: 1].

9. (Amended) [The] An inhibitor molecule [according to claim 2], which comprises a polymer of an inhibitor molecule according to [anyone] any one of claims 3 to [8]6, that contains 2 to 20 monomer units [of the amino acid sequence of interest derived from the amino acid sequence of either] from the amino acid sequence of P95/nucleolin, P40/PHAPIII [and, or] P30/PHAPI[, preferably 4 to 15 monomer units and more preferably 5 to 10 monomer units].

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10. (Amended) The inhibitor molecule according to [anyone] any one of claims [1 to] 2 to 6 or 9, which is [under the form of] a MAP matrix structure.

13. (Amended) A therapeutic composition comprising a pharmaceutically effective amount of an inhibitor molecule according to [anyone] any one of claims [1 to 12] 2 to 6 or 9 to 10, optionally in combination with another anti-HIV molecule [such as AZT].

23. (Amended) A method for screening an inhibitor according to [anyone] any one of claims 2 to [12] 6, 9 to 10, 13, or 22, comprising [the following steps]:

a) bringing into contact [cells] at least one cell expressing [the novel] an HIV receptor [according to the present invention] at [their] its surface with an amount of a HIV retrovirus equal to the [TCID₅₀] TCID₅₀;

b) incubating said [cells] at least one cell and retroviruses at 37°C during a period of time sufficient to allow the entry of the retrovirus within the [cells] at least one cell, in the presence of a defined amount of the compound to be assayed;

c) washing the [cells] at least one cell in order to remove the retroviruses that [has] have been absorbed onto the membranes of the [cells] at least one cell;

d) treating the [cells] at least one cell in order to eliminate the remaining extracellular retroviruses, for example by a controlled proteolysis with trypsin;

e) preparing cytoplasmic extracts by treating the [cells] at least one cell of step d) with an extraction buffer[, for example with a buffer] containing 20 mM Tris-HCl (pH7.6), 0.15 M NaCl, 5 mM [MgCl₂] MgCl₂, 0.2 mM PMSF, 100 U/ml aprotinin and 0.5% Triton X-100;

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- f) centrifuging the [cells] at least one cell obtained at step c), [for example] at 1000 g, and harvesting the supernatant medium, in order to separate the retroviral proteins;
- g) detecting and optionally measuring the concentration of the HIV proteins, either directly or indirectly[, for example by steric hindering].

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